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(71) Applicant *(for all designated States except US)*: SCHERING CORPORATION [US/US]; 2000 Galloping Hill Road, Kenilworth, NJ 07033 (US).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)* : SHIH, Neng-Yang [US/US]; 1 Maple Drive, North Caldwell, NJ 07006 (US).

(74) Agents: JEANETTE, Henry, C. et al.; Schering-Plough Corporation, Patent Department, M3W, One Giralda Farms, Madison, NJ 07940-1000 (US).

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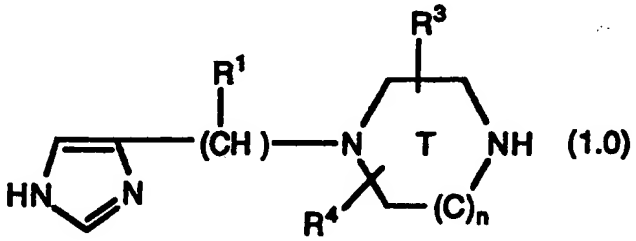
(54) Title: IMIDAZOLYL-ALKYL-PIPERAZINE AND -DIAZEPINE DERIVATIVES AS HISTAMINE H3 AGONISTS/ANTAGONISTS



(1.0)

(57) Abstract

Disclosed is a compound of formula (1.0) or a pharmaceutically acceptable salt r solvate thereof. Also disclosed are pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a compound of formula (1.0). Further disclosed is a method of treating allergy (for example asthma), inflammation, hypertension, raised intraocular pressure (such as glaucoma) - i.e., a method of lowering intraocular pressure, sleeping disorders, states f hyper and hypo motility and acidic secretion of the gastrointestinal tract, hypo and hyperactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimers, Schizophrenia, and migraine) comprising administering an effective amount of a compound of Formula (I) to a patient in need of such treatment.

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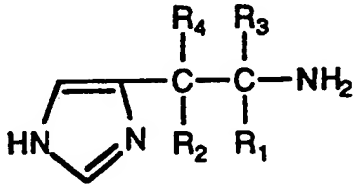
10 Imidazolyl-alkyl-piperazine and -diazepine derivatives as histamine H3 agonists/antagonists

BACKGROUND

15 H_3 receptor sites are known and are of current interest to those skilled in the art--for example, see: West, Jr. et al., "Biexponential Kinetics of (R)-α-[^{3}H]Methylhistamine Binding to the Rat Brain H_3 Histamine Receptor", Journal of Neurochemistry, Vol. 55, No. 5, pp. 1612-1616, 1990; West, Jr. et al., "Identification of Two H_3-Histamine
20 Receptor Subtypes", Molecular Pharmacology, 38:610-613; and Korte et al., "Characterization and Tissue Distribution of H_3 Histamine Receptors in Guinea Pigs by N^{α}-Methylhistamine", Biochemical and Biophysical Research Communications, Vol. 168, No. 3, pp. 979-986..

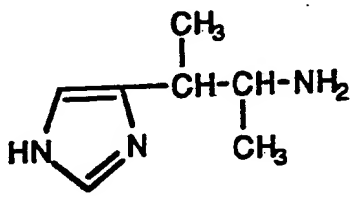
Arrang et al. in U.S. 4,767, 778 (Issued August 30, 1988)
25 disclose a pharmaceutical composition containing a histamine derivative of the formula:



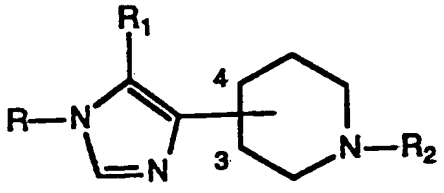
30 wherein each of R_1, R_2, and R_4, represents a hydrogen or a methyl, or R_1 and R_2 taken together represent a methylene, and R_3 is a hydrogen, a methyl or a carboxy, with the proviso that R_1, R_2, R_3, and R_4 are not

simultaneously methyl groups. It is disclosed that the derivatives behave as complete agonists of the H_3 receptors in rat brain and produce a maximal inhibition of release identical to that induced by histamine (approximately 60%). It is also disclosed that the histamine derivatives powerfully inhibit the release and synthesis of histamine by very selectively stimulating the H_3 receptors. Consequently, according to Arrang et al., the derivatives are likely to decrease histaminergic transmission in the digestive tract and in the nervous, cardiovascular and immune systems. Arrang et al. disclose that the derivatives can be used in therapy as a drug having sedative effects, as a sleep regulator, anticonvulsant, regulator of hypothalamo-hypophyseal secretion, antidepressant, and modulator of cerebral circulation. According to Arrang et al., inhibition of the release of inflammation messengers in various allergic conditions (e.g., asthma) is expected to result from stimulation of the H_3 receptors of the lung. It is further disclosed that the inhibition of release of gastric histamine is likely to exert antisecretory and antiulcerative effects. According to Arrang et al., modification of release of the messengers of immune responses is likely to modulate the latter responses.

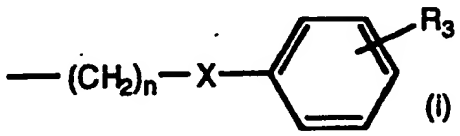
EP 0 338 939 discloses compounds of the formula:



Derwent abstract 86-273706/42 for EP 0 197 840 discloses imidazole derivatives of the formula:

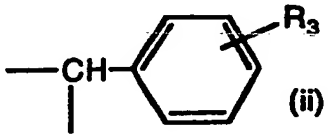


wherein R_1 is H, methyl or ethyl; R is H or R_2; and R_2 is 1-6C alkyl, piperonyl, 3-(benzimidazolon-1-yl)propyl, -CZ-NHR$_5$ or a group (i):



(i)

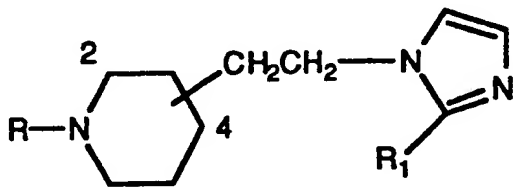
wherein n is 0-3; X is a bond, O, S, NH, CO, CH=CH or a group (ii):



(ii)

R_3 is H, methyl, halo, CN, CF_3 or COR_4; R_4 is 1-6C alkyl, 3-6C cycloalkyl or phenyl (optionally substituted by methyl or F); Z is O, S, NH, N-methyl or N-CN; and R_5 is 1-8C alkyl, 3-6C cycloalkyl (optionally substituted by phenyl), 3-6C cycloalkyl(1-3C)alkyl, phenyl (optionally substituted by methyl, halo or CF_3), phenyl(1-3C)alkyl, naphthyl, adamantyl or p-toluenesulphonyl. It is disclosed that these compounds are psychotropic agents. It is also disclosed that these compounds antagonise the histamine H3 receptors and increase the speed of cerebral histamine renewal.

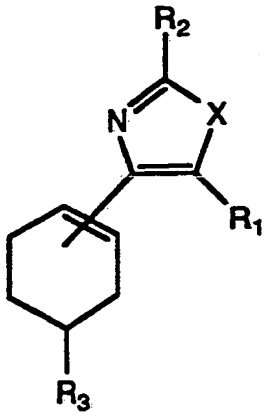
Derwent abstract 90-184730/24 for U.S. 4,925,851 discloses 2- or 4-(2-(1H-imidazol-1-yl)ethyl) piperidine compounds useful as antitumour agents for inhibiting lymphoma, sarcoma, myeloma and leukaemia. The compounds have the formula:



wherein R is -$CH_2(CH_2)_m$-Me, -CO-$(CH_2)_m$-Me or -CO-CMe_2-R_2; m is 2-18; R_2 is H or Me; R_1 is -$(CH_2)_n$-R_3; n is 0-13; R_3 is H, i-Pr or t-Bu; and

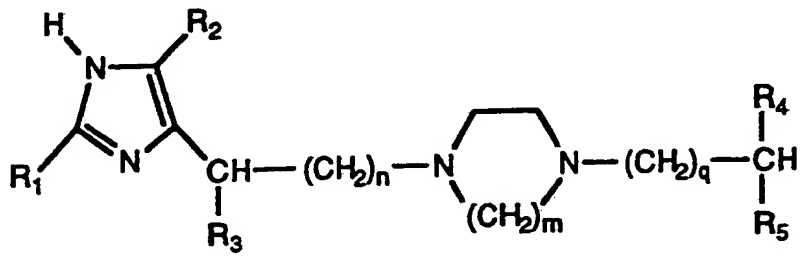
the floating group is at the 2- or 4- position; with the proviso that (1) the sum of C atoms in R_1 does not exceed 13; and (2) the sum of C atoms in R and R_1 does not exceed 25.

Derwent abstract 90-180087/24 for EP 372125A discloses compounds of the formula:



wherein X is O or S; R_1 is halo, CF_3, CN, NO_2, OH, or 1-6C alkoxy; R_2 is H, 1-6C alkyl, aryl, 7-13C aralkyl, optionally substituted amino or 5- or 6-membered N-containing ring; and R_3 is 1-6C hydrocarbyl, 7-13C aralkyl or 1-13C acyl. It is disclosed that these compounds have alpha2-antagonist activity with no dopamine activity and that they are useful for treating depression and other related illnesses (e.g., anxiety or cognitive disorders).

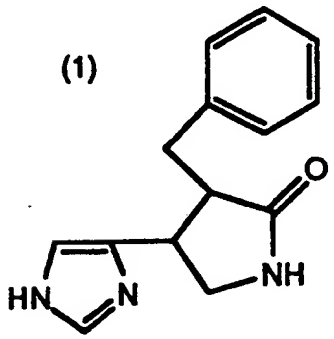
Derwent abstract 88-309195/44 for U.S. 4935417 discloses compounds of the formula:



wherein (according to U.S. 4935417) R^1 is aryl, lower alkyl, cycloalkyl or hydrogen; R^2 is aryl, lower alkyl or hydrogen; R^3 is lower alkyl, hydroxy or hydrogen; R^4 is aryl or hydrogen; R^5 is aryl or hydrogen; m is two or three; n is zero, one or two, provided that when R^3 is hydroxy, n is one or two; and q is zero, one, two or three. U.S. 4935417 discloses that these compounds are calcium channel antagonists useful for treating mammals having a variety of disease states, such as stroke, epilipsy, hypertension, angina, migraine, arrhythmia, thrombosis, embolism and also for treatment of spinal injuries

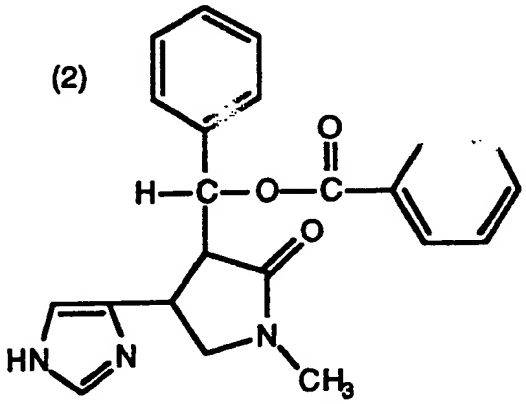
Compounds known in the art include:

(1)



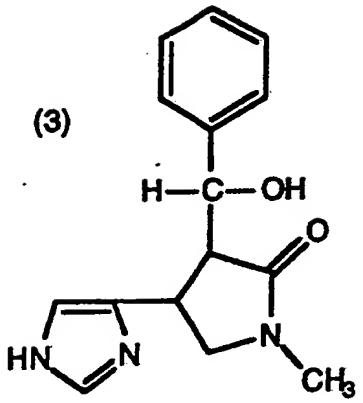
RN 85651-90-7
CA98(23):194919y

(2)



RN 81345-39-3
CA96(17):139642m

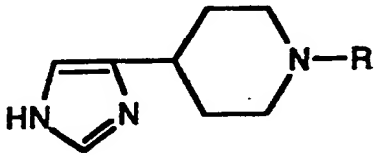
(3)



RN 81345-38-2
CA96(17):139642m

and

Known compounds in the art also include compounds of the formula:



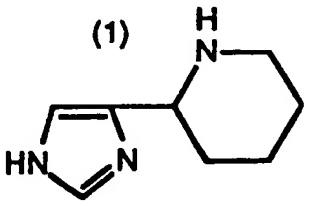
wherein R (Table 1) is:

TABLE 1

NO.	R	RN	CA
1	$-CH_3$	106243-44-1	106(11):84602r
2	$-CH(CH_3)_2$	106243-45-2	106(11):84602r
3	H	106243-23-6	106(11):84602r
4	$-C(S)NHC(CH_3)_2CH_2C(CH_3)$	106243-93-0	106(11):84602r
5	-C(O)NHCH(CH_3)(phenyl)	106243-90-7	---
6	-C(S)NH(p-chlorophenyl)	106243-85-0	---
7	-C(O)NH(phenyl)	106243-77-0	---
8	-C(NH)N(CH_3)(cyclopropyl)	106243-73-6	---
9	$-C(S)NHCH_3$	106243-61-2	---
10	$-CH_2CH_2$-phenyl	106243-49-6	---
11	$-CH_2CH_2$-p-flurophenyl	106243-67-8	---
12	benzyl	106243-25-8	---

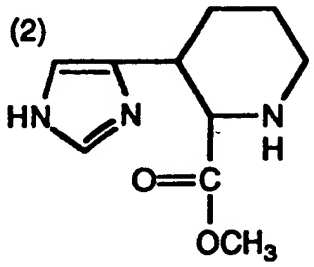
Additionally known compounds include:

(1)



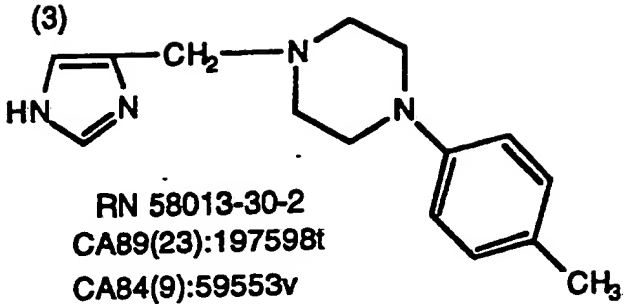
RN 51746-84-0
CA80(15):82801a

(2)



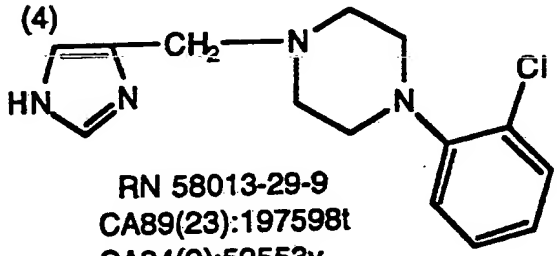
RN 67319-35-1
CA89(13):109229v

(3)



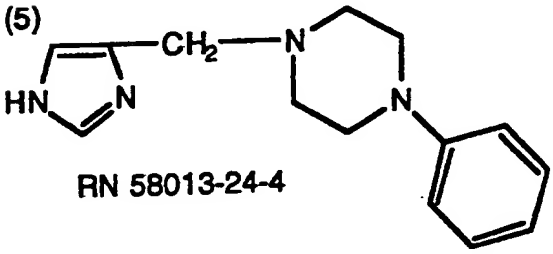
RN 58013-30-2
CA89(23):197598t
CA84(9):59553v

(4)



RN 58013-29-9
CA89(23):197598t
CA84(9):59553v

(5)



RN 58013-24-4

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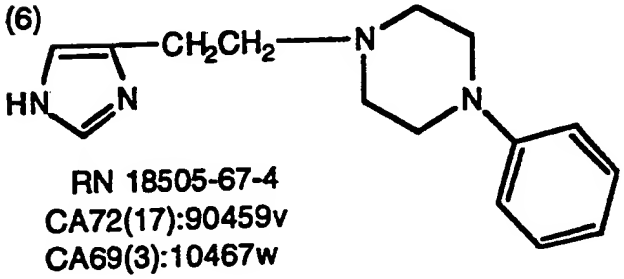
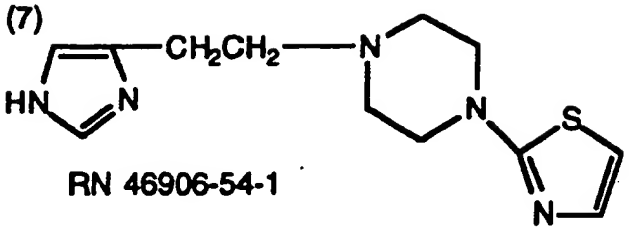


RN 18505-67-4
CA72(17):90459v
CA69(3):10467w

(7)



RN 46906-54-1

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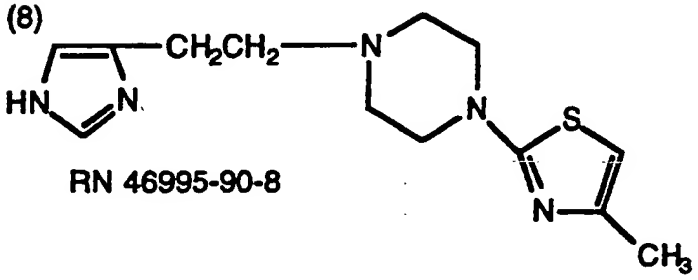
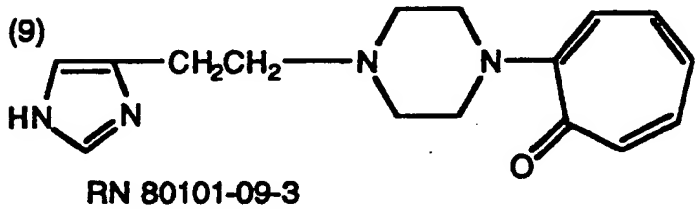


RN 46995-90-8

and

(9)

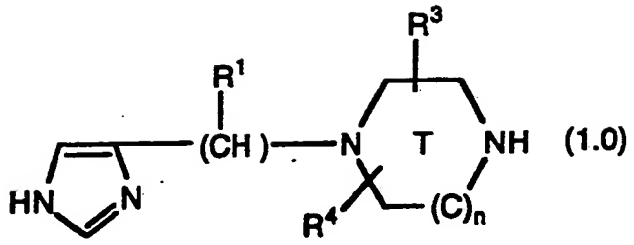


RN 80101-09-3
CA96(1):6760b

In view of the art's interest in compounds which effect the H_3 receptors, novel compounds having agonist or antagonist activity on H_3 receptors would be a welcome contribution to the art. This invention provides just such a contribution by providing novel compounds having H_3 agonist or antagonist activity.

SUMMARY OF THE INVENTION

This invention provides compounds of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) n is 1 or 2, such that when n is 1 then ring T is a six membered ring, and when n is 2 then ring T is a seven membered ring;

(B) R^1 is selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) allyl; and

(4) propargyl;

(C) R^3 and R^4 are independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) allyl;

(4) propargyl; and

(5) $-(CH_2)_q-R^5$ wherein q is an integer of: 1 to 7, and R^5 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^6$, $-C(O)OR^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, CN and $-SR^6$ wherein R^6 and R^7 are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl, $-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^6 and R^7 are each independently selected from the group consisting of: H and C_1 to C_6 alkyl; and

(E) R^3 and R^4 are each independently bound to the same or different carbon atom of ring T.

Those skilled in the art will appreciate that the total number of substituents on each $-(C)_n-$ is two , and that such substituents are independently selected from the group consisting of H, R^3, and R^4, such that there is only one R^3 and one R^4 substituent in ring T.

This invention also provides pharmaceutical compositions comprising a pharmaceutically acceptable carrier and an effective amount of a Compound of Formula 1.0.

This invention further provides a method of treating allergy, (for example asthma), inflammation, hypertension, raised intraocular pressure (such as glaucoma)--i.e., a method of lowering intraocular pressure, sleeping disorders (e.g., hypersomnia, somnolence, narcolepsy and sleeplessness, such as insomnia), states of hyper and hypo motility and acidic secretion of the gastrointestinal tract, hypo and hyperactivity of the central nervous system (for example, agitation and depression) and other CNS disorders (such as Alzheimers, Schizophrenia, and migraine) comprising administering an effective amount of a compound of Formula I to a patient in need of such treatment.

DETAILED DESCRIPTION OF THE INVENTION

As used herein the following terms have the following meanings unless indicated otherwise:

alkyl - represents a straight or branched, saturated hydrocarbon chain having from 1 to 6 carbon atoms;

cycloalkyl - represents a saturated carbocyclic ring having from 3 to 6 carbon atoms;

halogen (halo) - represents fluoro, chloro, bromo or iodo;

DMF - stands for N, N,-dimethylformamide;

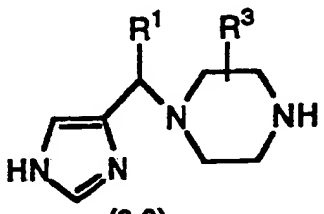
SEM - stands for 2-(trimethylsilyl)ethoxym thyl; and

THF - stands for tetrahydrofuran.

Also, unless stated otherwise, the substituents for the various embodiments described below are as defined for Formula 1.0.

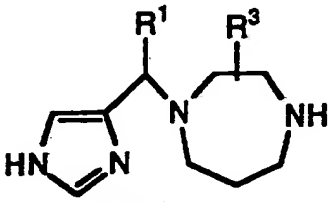
In the compounds of this invention, preferably R^3 and R^4 are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, allyl, propargyl, and $-(CH_2)_q-R^5$ wherein R^5 is phenyl or substituted phenyl. Most preferably, R^1, R^3 and R^4 are each independently selected from the group consisting of H and C_1 to C_6 alkyl. More preferably, R^1, R^3 and R^4 are each independently selected from H and methyl. Preferably, R^1, R^3 and R^4 are H.

Representative compounds of this invention include compounds of the formula:



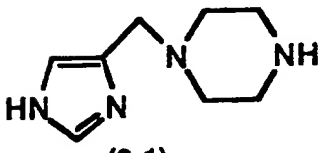
(2.0)

; and



(4.0)

Representative compounds of Formula 1.0 include:



(2.1)

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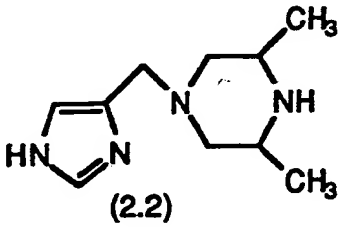

(2.2)

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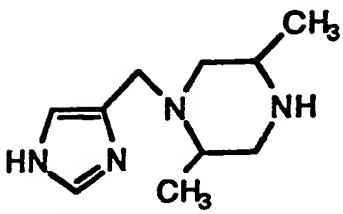
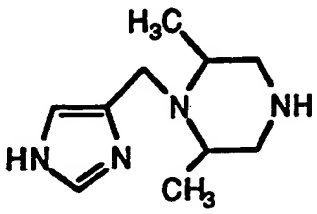


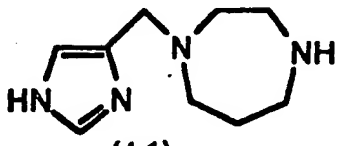
(2.3)

; and



(2.4)

Representative compounds of Formula 1.0 also include:



(4.1)

Certain compounds of the invention may exist in different isomeric (e.g., enantiomers and diastereoisomers) forms. The invention contemplates all such isomers both in pure form and in admixture, including racemic mixtures. Enol forms are also included.

The compounds of Formula 1.0 can exist in unsolvated as well as solvated forms, including hydrated forms, e.g., hemi-hydrate. In general, the solvated forms, with pharmaceutically acceptable solvents such as water, ethanol and the like are equivalent to the unsolvated forms for purposes of the invention.

Certain basic compounds of the invention also form pharmaceutically acceptable salts, e.g., acid addition salts. For example, the nitrogen atoms may form salts with acids. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, malic, fumaric, succinic, ascorbic, maleic, methanesulfonic and other mineral and carboxylic acids well known to those in the art. The salts are prepared by contacting the free base form with a sufficient amount of the desired acid to produce a salt in the conventional manner. The free base forms may be regenerated by treating the salt with a suitable dilute aqueous base solution such as dilute aqueous sodium hydroxide, potassium carbonate, ammonia and sodium bicarbonate. The free base forms differ from their respective salt forms somewhat in certain physical properties, such as solubility in polar solvents, but the acid and base salts are otherwise equivalent to their respective free base forms for purposes of the invention.

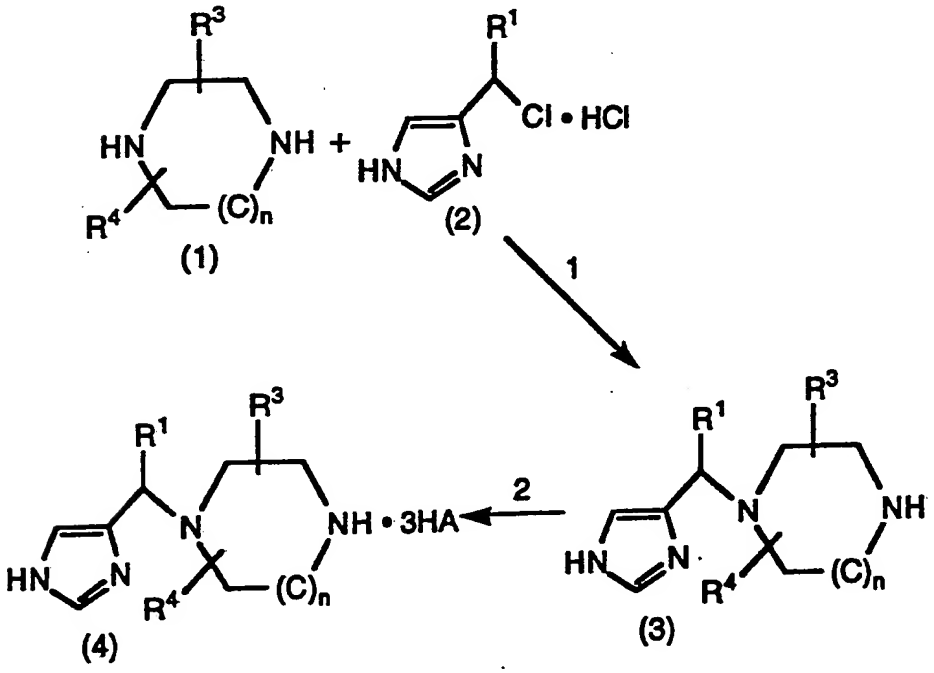
All such acid and base salts are intended to be pharmaceutically acceptable salts within the scope of the invention and

all acid and base salts are considered equivalent to the free forms of the corresponding compounds for purposes of the invention.

The following processes may be employed to produce compounds of Formula 1.0. Unless stated otherwise, reactions are conducted at an appropriate temperature which allows the reaction to proceed at a reasonable rate to completion.

A PREPARATION OF COMPOUNDS WHEREIN m IS 1

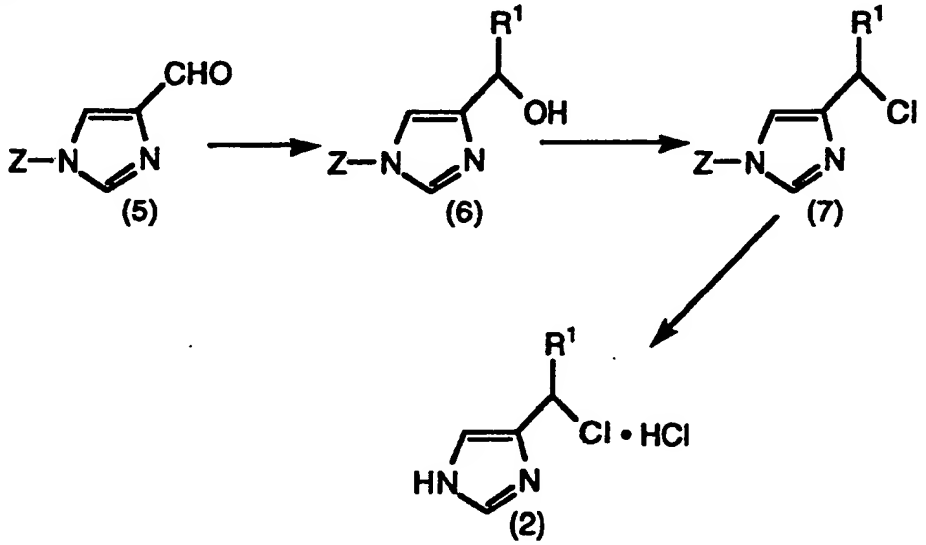
SCHEME 1



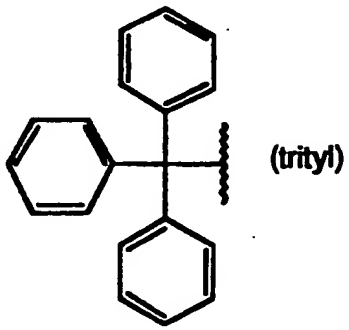
In Step 1 of Scheme 1, compound (1), wherein n is 1 or 2, is reacted with compound (2) at a temperature of about 20 to about 80°C in an organic solvent to produce compound (3). Preferably, ethanol is used as the organic solvent, but other suitable solvents include methanol, propyl alcohol and the like.

In Step 2 of Scheme 1, compound (3) is then dissolved in an aqueous acid to form a salt, compound (4). Examples of aqueous acids include HCl, HBr, H_2SO_4 and the like. Preferably HCl is employed (i.e., in compound (4) HA is HCl). The above reaction is conducted at a temperature of about -20 to about 20°C. Alternatively, compound (3) is reacted with di-t-butyl-dicarbonate in an organic solvent (e.g., DMF, CH_2Cl_2 and the like) at a temperature of about 0 to about 50°C, and the reaction product (compound (3) wherein the NH groups of the imidazole and the cyclic amine are protected with -C(O)O(t-butyl)) is then reacted with aqueous acid at a temperature of about -20 to about 20°C to produce compound (4).

Compound (2) is prepared is three steps from Compound (5):



Z represents the protecting group:



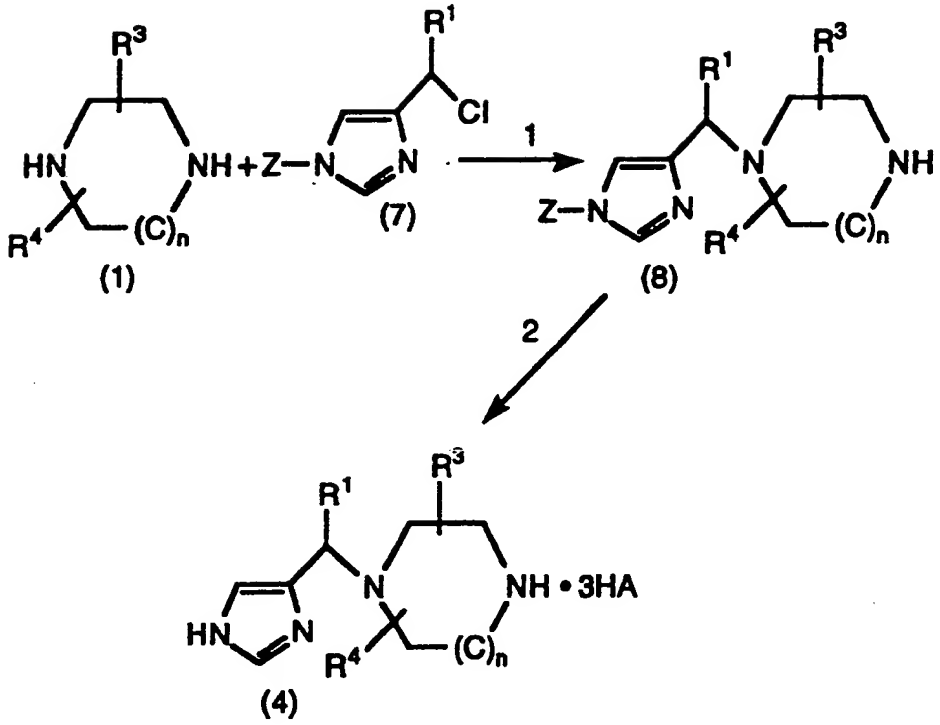
Z can be other groups, such as 2-(trimethylsilyl)ethoxymethyl, benzyloxycarbonyl and the like; however, unless stated otherwise, Z preferably represents the trityl group in the processes as described below for making the compounds of this invention.

Those skilled in the art will appreciate that other protecting groups known in the art may be used--such as, for example, base sensitive groups wherein the protected compounds would be deprotected using basic conditions (e.g., NaOH). The processes described herein wherein the protected compound is deprotected under acidic conditions may also be carried out under basic conditions when a base sensitive protecting group is used.

Compound (5) is reacted with an organometallic reagent R^1M, wherein M is Li or MgBr, to produce compound (6). The reaction takes place in an inert organic solvent at a temperature of about -78 to 0°C. Suitable inert organic solvents include: THF, diethyl ether and the like. Compound (6) is then reacted with thionyl chloride in an inert organic solvent such as benzene or CH_2Cl_2, in the presence of base to generate compound (7). The reaction is conducted at a temperature of about -20 to 80°C. Suitable bases include: pyridine, triethylamine and the like. Preferably, triethylamine is used as the amine base. Compound (7) is then deprotected with dilute aqueous acid, such as HCl or HBr, at a temperature of about 50 to about 90°C to produce compound (2). Other protecting groups are removed by methods known in the art. Compound (5) can be obtained by following the literature procedure set forth in J.K. Kelly, et al., J. Med. Chem, 20, 721(1977).

B. PREPARTION OF COMPOUNDS WHEREIN m IS 1

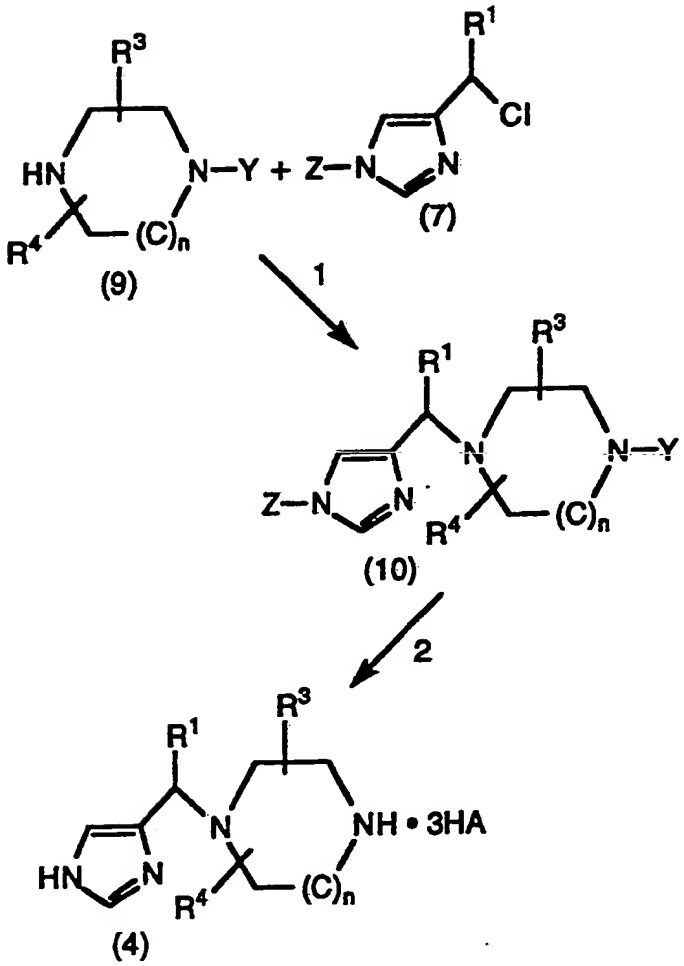
SCHEME 2



In Step 1 of Scheme 2, compound (8) is produced by reacting compound (1) with compound (7) in an inert organic solvent at a temperature of about 20 to about 80°C. Suitable organic solvents include THF, DMF, ethanol and the like. Preferably THF is used as the organic solvent. The reaction can be conducted with or without amine base. Suitable bases include triethylamine and the like. Compound (8) is then deprotected with dilute aqueous acid (HA) at a temperature of about 50 to about 90°C to generate compound (4). Suitable aqueous acids include HCl, HBr, and the like.

C. PREPARATION OF COMPOUNDS WHEREIN m IS 1

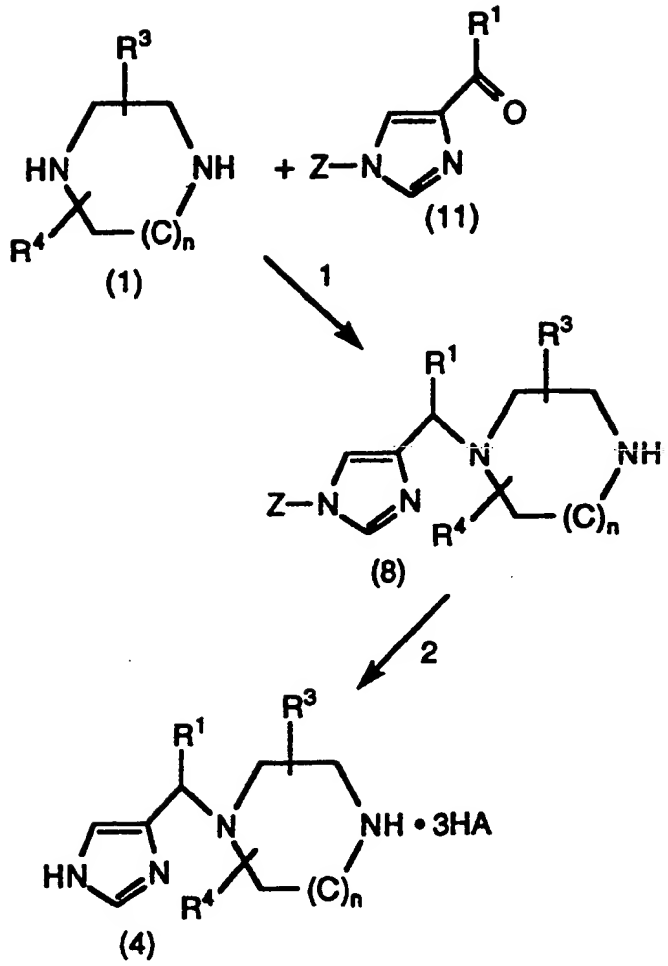
SCHEME 3



By following the steps in Scheme 2, with the exception that compound (9) (wherein n is 1 or 2, and Y is a protecting group such as trityl, $-CO_2C(CH_3)_3$, or SEM group) is used instead of compound (1), compound (4) is produced.

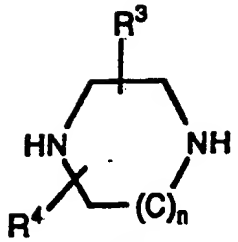
D. PREPARATION OF COMPOUNDS WHEREIN m IS 1

SCHEME 4



In Step 1 of Scheme 4, compound (11) is reacted with compound (1), in an inert organic solvent and in the presence of a reducing agent, to produce compound (8). The reaction can be conducted at a temperature of about -20 to about 50°C. Methanol is the preferred organic solvent; however, other suitable solvents include ethanol, DMF and the like. Suitable reducing agents include $NaBH_3CN$, $NaBH_4$, and Pd/C. When the latter (Pd/C) is employed as the reducing agent, the reaction is conducted under H_2 atmosphere. The conversion of compound (8) to compound (4) is accomplished by following the same procedure described above in Step 2 of Scheme 2.

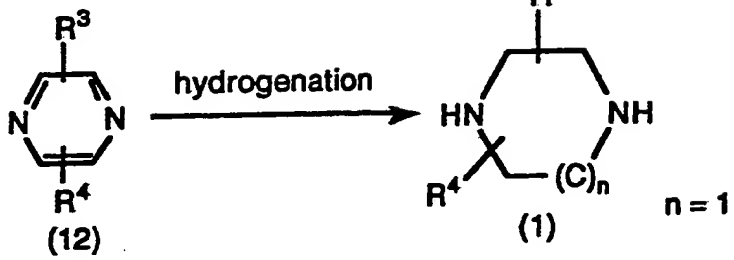
Compound (1)



(1)

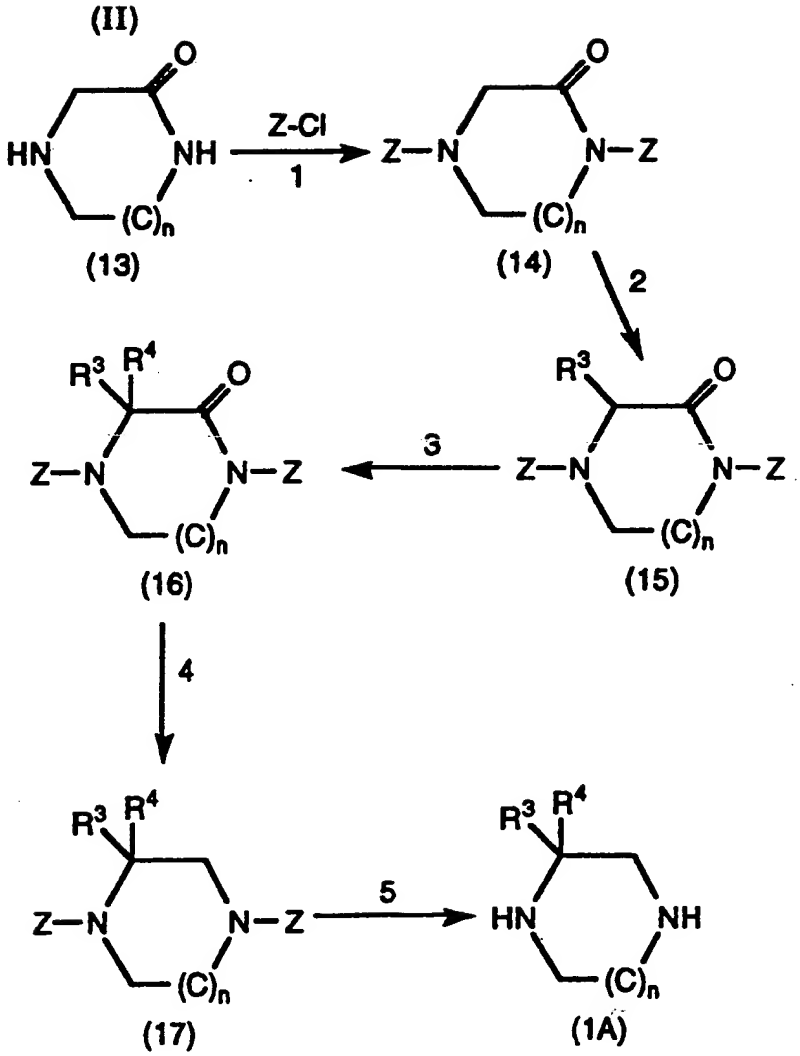
may be prepared by:

(I)



(12) (1) n = 1

The hydrogenation of compound (12) is carried out using Pd-black as the catalyst, in an organic solvent, e.g., ethanol, methanol, THF and the like, using a temperature of about 20 to about 100°C, under a hydrogen at a pressure of about 1 to about 10 atmospheres.



In Step (1) of (II), compound (13) is reacted with Z-Cl in an organic solvent in the presence of a base to produce compound (14). The reaction is carried out at a temperature of about 0 to about 70°C. Examples of suitable bases include NaH, KH and the like. Suitable solvents include THF, DMF and the like. Z represents trityl or $(CH_3)_3CSi(CH_3)_2$-.

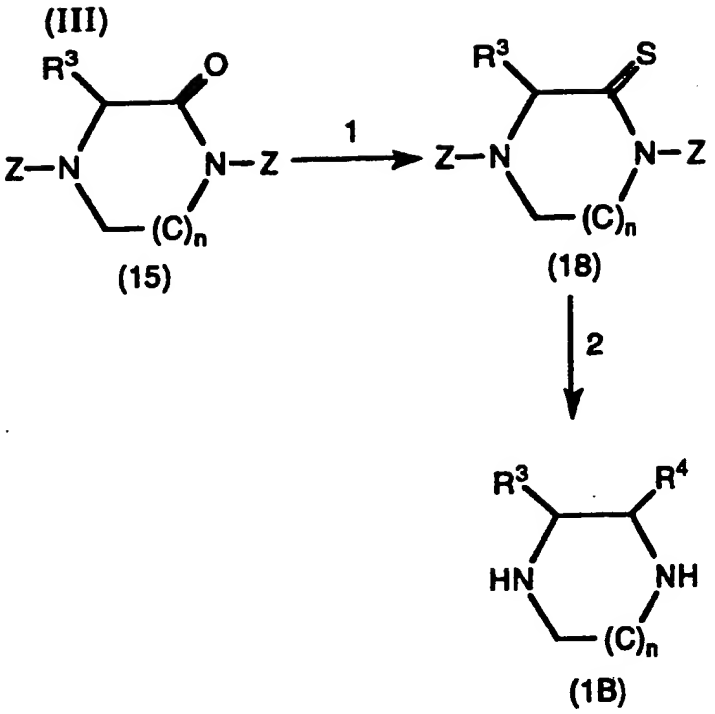
In Step (2) of (II), the anion of compound (14) is reacted with R^3-L in an organic solvent to produce compound (15). The reaction is carried out at a temperature of about -78 to about 50°C. Examples of

solvents include THF, 1,4-dioxane and the like. L represents a leaving group, such as, for example, Cl, Br, I and the like. The anion of compound (14) is generated by reacting compound (14) with a base, such as LDA, KH and the like.

In Step (3) of (II), the anion of compound (15) is reacted with R^4-L in an organic solvent to produce compound (16). The reaction is carried out at a temperature of about -78 to about 50°C. Examples of solvents include THF, 1,4-dioxane and the like. L represents a leaving group, such as, for example, Cl, Br, I and the like. The anion of compound (15) is generated by reacting compound (15) with a base, such as LDA, KH and the like.

In Step (4) of (II), compound (16) is reduced with $LiAlH_4$ to produce compound (17). The reduction takes place in an organic solvent, such as THF, 1,4-dioxane and the like, and at a temperature of about 20 to about 100°C.

In Step (5) of (II), compound (17) is deprotected, to produce compound (1A), using aqueous acid, such as HCl, HBr, HI and the like. The deprotection step is carried out at a temperature of about 25 to about 100°C in an organic solvent, such as 1,2-dichloroethane, ethanol and the like.



In Step (1) of (III), compound (15) is reacted with lawesson's reagent to produce compound (18). The reaction is carried out at a temperature of about 50 to about 120°C in an organic solvent, such as toluene, benzene and the like.

In Step (2) of (III), compound (18) is reacted with R^4M, wherein M represents Li or the grignard reagent MgX (X represents halogen), which is then followed by reaction with $LiAlH_4$ to produce compound (1). A similar reaction is described in Tet. Letters, 28, 1529 (87).

In the above processes, it is sometimes desirable and/or necessary to protect certain groups during the reactions. Certain protecting groups are employed in the above processes but, as those skilled in the art will recognize, other protecting groups may be used in their place. Conventional protecting groups are operable as described in Greene, T.W., and Wuts, P.G.M., "Protective Groups In Organic Synthesis," John Wiley & Sons, New York, 1991; the disclosure of which is incorporated herein by reference thereto. After the reaction or

reactions, the protecting groups may be removed by standard procedures.

The compounds of this invention are either agonists or antagonists of the histamine H_3 receptor. The binding affinity of the compounds of the invention to the H_3 receptor may be demonstrated by the procedure described below:

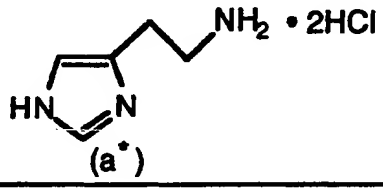
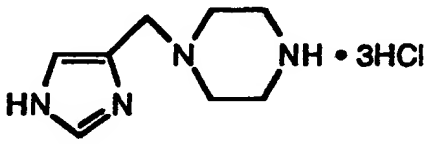
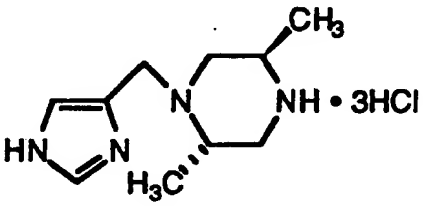
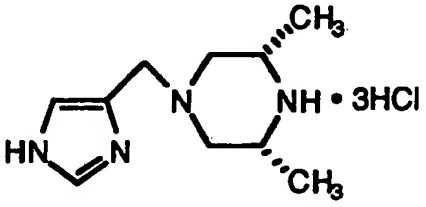
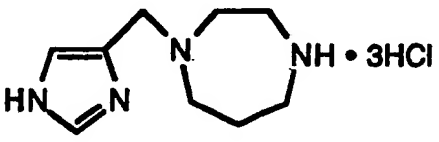
H_3 Receptor Binding Assay

The source of the H_3 receptors in this experiment was guinea pig brain. The animals used weighed 400-600 g. The tissue was homogenized using a Polytron in a solution of 50 mM Tris, pH 7.5. The final concentration of tissue in the homogenization buffer was 10% w/v. The homogenates were centrifuged at 1000 x g for 10 min. in order to remove clumps of tissue and debris. The resulting supernatants were then centrifuged at 50,000 x g for 20 min. in order to sediment the membranes, which were next washed 3 times in homogenization buffer (50,000 x g for 20 min. each). The membranes were frozen and stored at -70°C until needed.

All compounds to be tested were dissolved in DMSO and then diluted into the binding buffer (50 mM Tris, pH 7.5) such that the final concentration was 2 µg/mL with 0.1% DMSO. Membranes were then added (400 µg of protein) to the reaction tubes. The reaction was started by the addition of 3 nM [^{3}H]R-α-methylhistamine (8.8 Ci/mmol) or [^{3}H]-N-methylhistamine (80 Ci/mmol) and incubated at 30° for 30 min. Bound ligand was separated from unbound ligand by filtration, and the amount of radioactive ligand bound to the membranes was quantitiated by liquid scintillation spectrometry. All incubations were performed in duplicate and the standard error was less than 10% in all instances. Compounds that inhibited greater than 70% of the specific binding of radioactive ligand to the receptor were serially diluted to determine a K_i (µM). The results are given in Table 2.

In Table 2, the compound represented by (a*) is known in the art.

TABLE 2

COMPOUND	H_3 Binding K_i(μM)
 (a*)	0.014
	0.0047
	6%
	24%
	0.087

For preparing pharmaceutical compositions from the compounds described by this invention, inert, pharmaceutically

acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets and suppositories. The powders and tablets may be comprised of from about 5 to about 70 percent active ingredient. Suitable solid carriers are known in the art, e.g. magnesium carbonate, magnesium stearate, talc, sugar, lactose. Tablets, powders, cachets and capsules can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax such as a mixture of fatty acid glycerides or cocoa butter is first melted, and the active ingredient is dispersed homogeneously therein as by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

Liquid form preparations include solutions, suspensions and emulsions. As an example may be mentioned water or water-propylene glycol solutions for parenteral injection.

Liquid form preparations may also include solutions for intranasal administration.

Aerosol preparations suitable for inhalation may include solutions and solids in powder form, which may be in combination with a pharmaceutically acceptable carrier, such as an inert compressed gas.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for either oral or parenteral administration. Such liquid forms include solutions, suspensions and emulsions.

The compounds of the invention may also be deliverable transdermally. The transdermal compositions can take the form of creams, lotions, aerosols and/or emulsions and can be included in a transdermal patch of the matrix or reservoir type as are conventional in the art for this purpose.

Preferably the compound is administered orally.

Preferably, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component, e.g., an effective amount to achiev the desired purpose.

The quantity of active compound in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, more preferably from about 1 mg to 500 mg, according to the particular application.

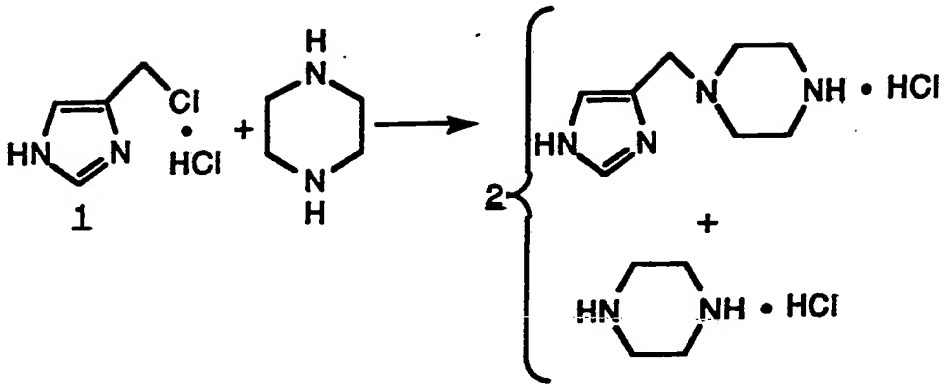
The actual dosage employed may be varied depending upon the requirements of the patient and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

The amount and frequency of administration of the compounds of the invention and the pharmaceutically acceptable salts thereof will be regulated according to the judgment of the attending clinician considering such factors as age, condition and size of the patient as well as severity of the symptoms being treated. A typical recommended dosage regimen is oral administration of from 1 mg to 2000 mg/day preferably 10 to 1000 mg/day, in one to four divided doses to achieve relief of the symptoms. The compounds are non-toxic when administered within this dosage range.

The invention disclosed herein is exemplified by the following examples, which should not be construed to limit the scope of the disclosure. Alternative mechanistic pathways and analogous structures within the scope of the invention may be apparent to those skilled in the art.

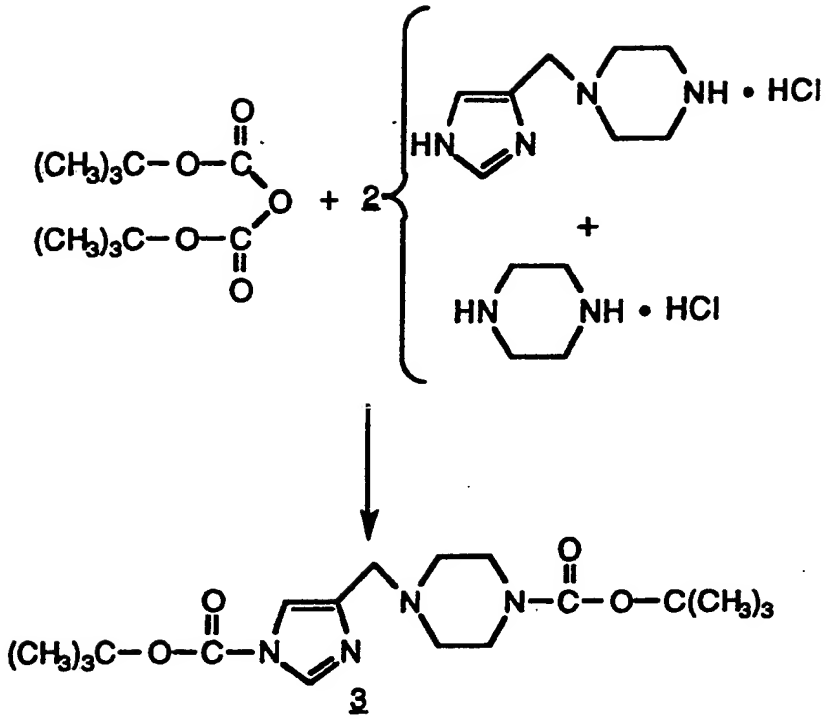
EXAMPLE 1

A.



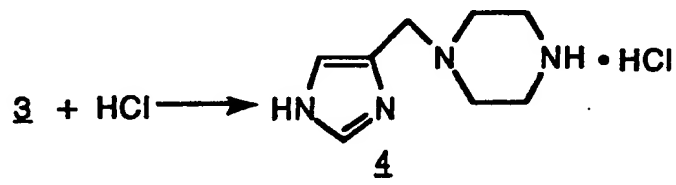
To a refluxing solution of 8.6 g of piperidine in 50 mL of absolute ethanol was added a solution of 1.53 g of 4-chloromethylimidazole hydrochloride (1) in 10 mL of absolute ethanol for over 1.5 hr. After an additional 2 hours of refluxing, the reaction mixture was cooled and the ethanol and excess piperidine were removed by vacuum distillation. The residue (2) was used directly in Step B (below).

B.



To a mixture of the residue 2 in 70 mL of anhydrous DMF was added 19 mL of triethylamine and 21 mL of di-t-butyl-dicarbonate at room temperature under nitrogen. The resulting mixture was stirred for 29 hours, and then it was filtered. The filtrate was concentrated under vacuum and the residue was purified by flash chromatography on silica gel to give 1.73 g of the compound of formula 3 (50% yield from 1), which was recrystallized in ethyl acetate. MS (FAB) 367 (M+1).

C.

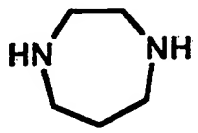
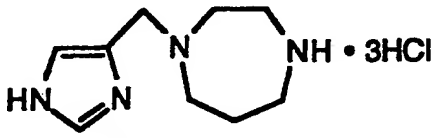
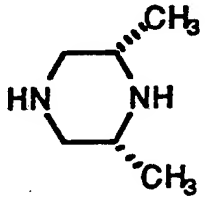
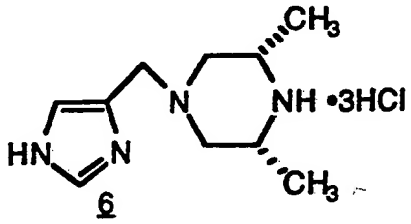
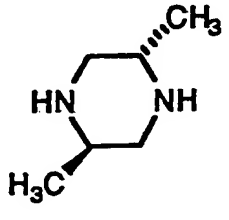
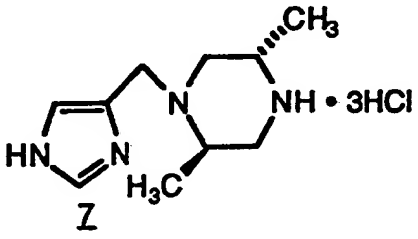


A stirring solution of 1.2 g of compound of formula 3 in 20 mL of ethyl acetate was cooled to 0°C, and dry HCl gas was bubbled in

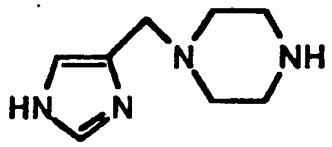
for 1 hour. The solid precipitate that resulted was filtered and recrystallized in methanol to give 0.75 g of the compound of formula 4 (80 % yield). MS (EI) 166 (M^+).

Following the procedure described above in Steps A to C of Example 1, and using the starting compounds set forth in Table 3, compounds 5 to 7 were prepared.

TABLE 3

STARTING COMPOUND	PRODUCT	MS (m/z)
	 5	(EI) 180 (M^+)
	 6	(CI) 195 (M+1)
	 7	(CI) 195 (M+1)

The following are examples of pharmaceutical dosage forms which contain a compound of the invention. As used therein, the term "active compound" is used to designate the compound



The scope of the invention in its pharmaceutical composition aspect is not to be limited by the examples provided, since any other compound of structural formula 1.0 can be substituted into the pharmaceutical composition examples.

Pharmaceutical Dosage Form Examples

EXAMPLE A
Tablets

No.	Ingredients	mg/tablet	mg/tablet
1.	Active compound	100	500
2.	Lactose USP	122	113
3.	Corn Starch, Food Grade, as a 10% paste in Purified Water	30	40
4.	Corn Starch, Food Grade	45	40
5.	Magnesium Stearate	3	7
	Total	300	700

Method of Manufacture

Mix Item Nos. 1 and 2 in a suitable mixer for 10–15 minutes. Granulate the mixture with Item No. 3. Mill the damp granules

through a coarse screen (e.g., 1/4", 0.63 cm) if necessary. Dry the damp granules. Screen the dried granules if necessary and mix with Item No. 4 and mix for 10–15 minutes. Add Item No. 5 and mix for 1–3 minutes. Compress the mixture to appropriate size and weigh on a suitable tablet machine.

EXAMPLE B

Capsules

No.	Ingredient	mg/capsule	mg/capsule
1.	Active compound	100	500
2.	Lactose USP	106	123
3.	Corn Starch, Food Grade	40	70
4.	Magnesium Stearate NF	4	7
	Total	250	700

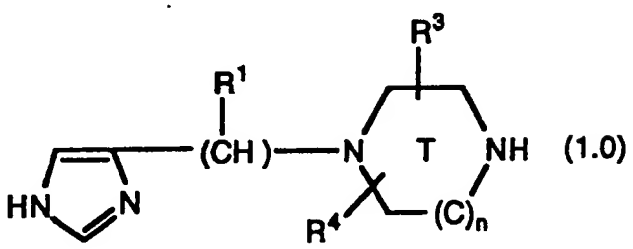
Method of Manufacture

Mix Item Nos. 1, 2 and 3 in a suitable blender for 10-15 minutes. Add Item No. 4 and mix for 1-3 minutes. Fill the mixture into suitable two-piece hard gelatin capsules on a suitable encapsulating machine.

While the present invention has been described in conjunction with the specific embodiments set forth above, many alternatives, modifications and variations thereof will be apparent to those of ordinary skill in the art. All such alternatives, modifications and variations are intended to fall within the spirit and scope of the present invention.

WHAT IS CLAIMED IS:

1. A compound of the formula:



(1.0)

or a pharmaceutically acceptable salt or solvate thereof, wherein:

(A) n is 1 or 2, such that when n is 1 then ring T is a six membered ring, and when n is 2 then ring T is a seven membered ring;

(B) R^1 is selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) allyl; and

(4) propargyl;

(C) R^3 and R^4 are independently selected from the group consisting of:

(1) H;

(2) C_1 to C_6 alkyl;

(3) allyl;

(4) propargyl; and

(5) $-(CH_2)_q-R^5$ wherein q is an integer of: 1 to 7, and R^5 is selected from the group consisting of: phenyl, substituted phenyl, $-OR^6$, $-C(O)OR^6$, $-C(O)R^6$, $-OC(O)R^6$, $-C(O)NR^6R^7$, CN and $-SR^6$ wherein R^6 and R^7 are as defined below, and wherein the substituents on said substituted phenyl are each independently selected from the group consisting of: -OH, -O-(C_1 to C_6)alkyl, halogen, C_1 to C_6 alkyl,

$-CF_3$, -CN, and $-NO_2$, and wherein said substituted phenyl contains from 1 to 3 substituents;

(D) R^6 and R^7 are each independently selected from the group consisting of: H and C_1 to C_6 alkyl; and

(E) R^3 and R^4 are each independently bound to the same or different carbon atom of ring T.

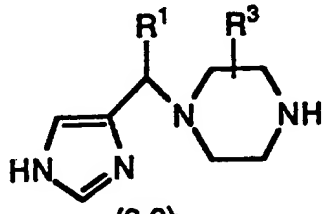
2. The compound of Claim 1 wherein R^3 and R^4 are each independently selected from the group consisting of: H, C_1 to C_6 alkyl, allyl, propargyl, and $-(CH_2)_q-R^5$ wherein R^5 is phenyl or substituted phenyl.

3. The compound of Claim 1 wherein R^1, R^3 and R^4 are each independently selected from the group consisting of H and C_1 to C_6 alkyl.

4. The compound of Claim 3 wherein R^1, R^3 and R^4 are each independently selected from H and methyl.

5. The compound of Claim 1 wherein n is 1.

6. The compound of Claim 1 wherein said compound is selected from the group consisting of compounds having the formula:



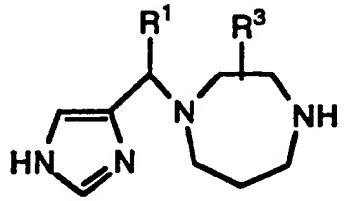
(2.0)

wherein R^1 and R^3 are as defined in Claim 1.

7. The compound of Claim 6 wherein R^1 and R^3 are each independently selected from the group consisting essentially of: H, and C_1 to C_6 alkyl.

8. The compound of Claim 7 wherein R^1 and R^3 are each independently selected from H and methyl.

9. The compound of Claim 1 wherein said compound is selected from the group consisting of compounds having the formula:



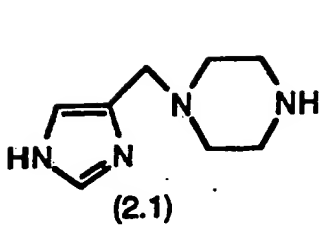
(4.0)

wherein R^1 and R^3 are as defined in Claim 1.

10. The compound of Claim 9 wherein R^1 and R^3 are each independently selected from the group consisting essentially of: H, and C_1 to C_6 alkyl.

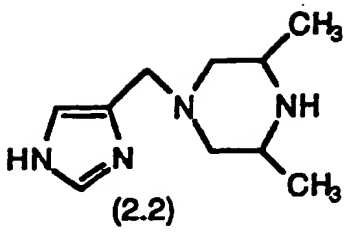
11. The compound of Claim 10 wherein R^1 and R^3 are each independently selected from H and methyl.

12. The compound of Claim 1 wherein said compound is selected from the group consisting of compounds having the formula:



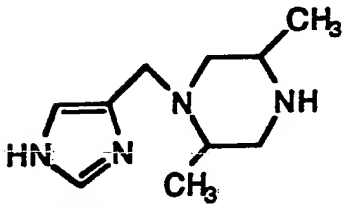
(2.1)

;

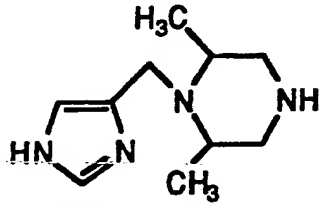


(2.2)

;

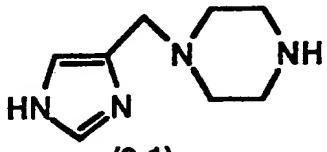


(2.3)



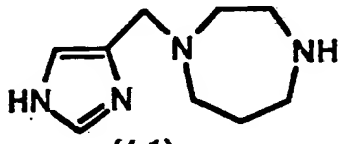
; and (2.4)

13. A compound having the formula:



(2.1)

14. A compound having the formula:



(4.1)

15. A pharmaceutical composition, for use in treating allergy, inflammation, hypertension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimers, Schizophrenia, and migraines, comprising a pharmaceutically acceptable carrier and an effective amount of a Compound of Claim 1.

16. A method of treating allergy, inflammation, hypertension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimers, Schizophrenia, and migraines comprising administering an effective amount of a compound of Claim 1 to a patient in need of such treatment.

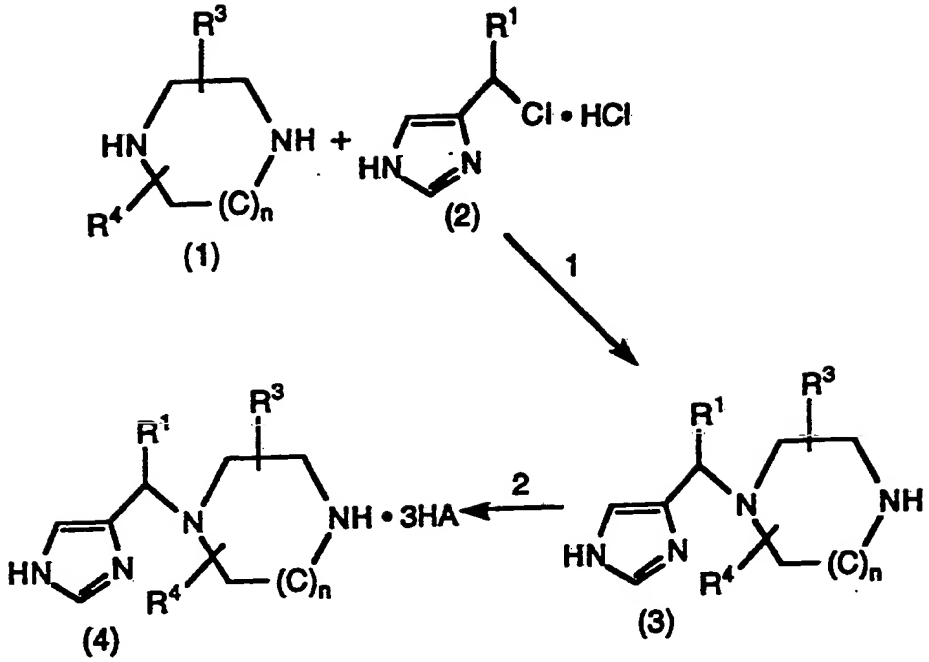
17. The use of a compound of Claim 1 for the manufacture of a medicament for use in treating allergy, inflammation, hypertension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimers, Schizophrenia, and migraines.

18. The use of a compound of Claim 1 for the treatment of allergy, inflammation, hypertension, glaucoma, sleeping disorders, states of hyper and hypo motility of the gastrointestinal tract, hypo and hyperactivity of the central nervous system, Alzheimers, Schizophrenia, and migraines.

19 A method of preparing a pharmaceutical composition comprising admixing a compound of Claim 1 with a pharmaceutically acceptable carrier.

20. A process for preparing compounds of Claim 1 comprising:

(A) Scheme 1

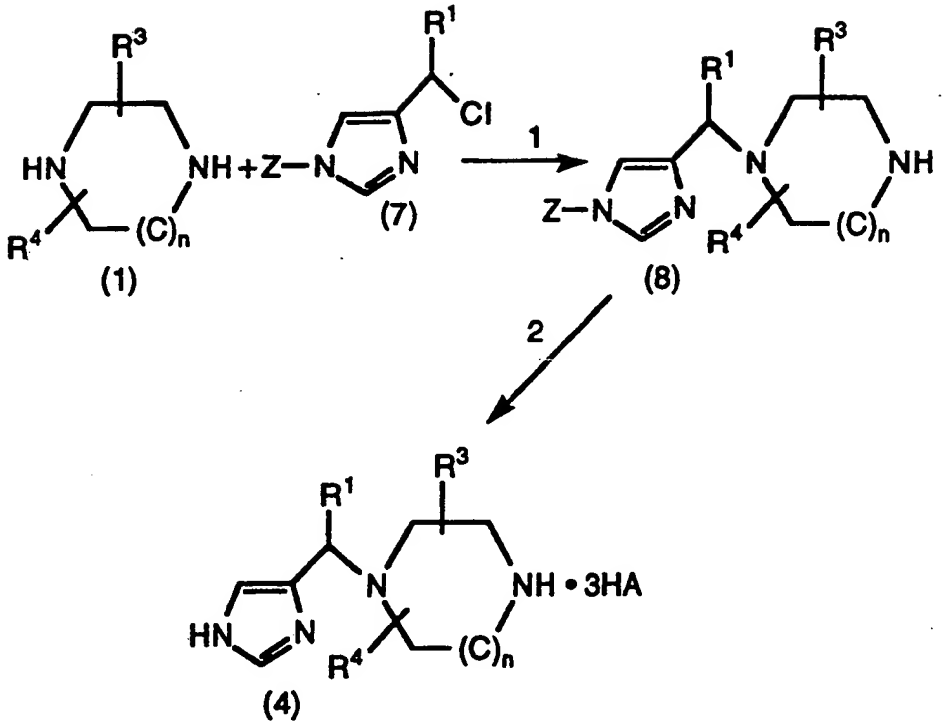


1) reacting compound (1) with compound (2) at a temperature of about 20 to about 80°C in an organic solvent to produce compound (3); and

2) (a) dissolving compound 3) in an aqueous acid to form compound (4), the reaction being conducted at a temperature of about -20 to about 20°C; or

(b) reacting compound (3) with di-t-butyl-dicarbonate in an organic solvent at a temperature of about 0 to about 50°C, and then reacting the reaction product with an aqueous acid at a temperature of about -20 to about 20°C to produce compound (4);

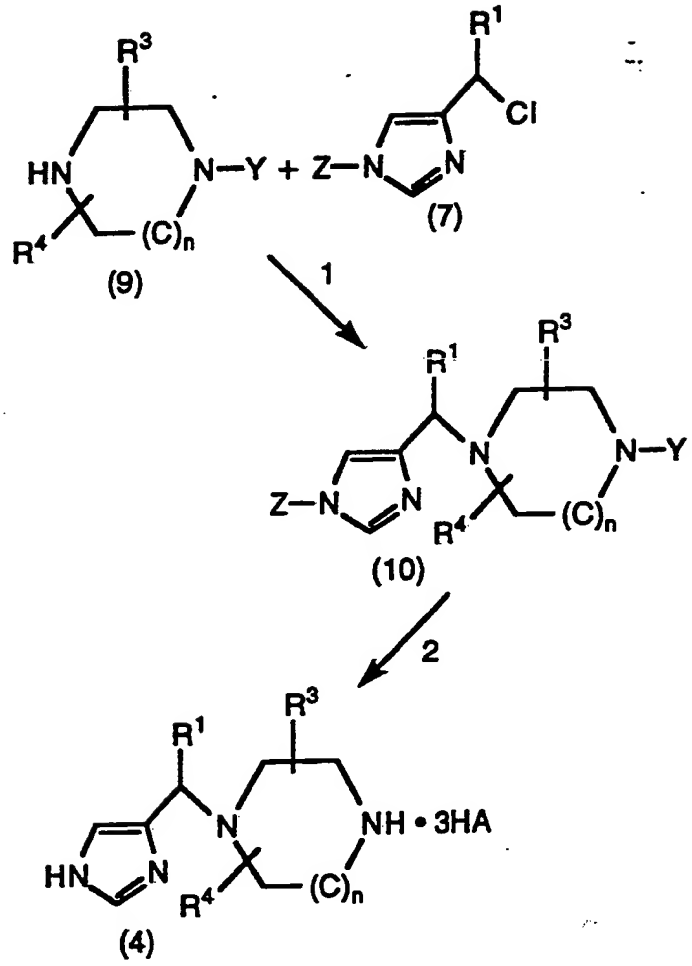
(B) Scheme 2



1) reacting compound (1) with compound (7) in an inert organic solvent at a temperature of about 20 to about 80°C to produce compound (8); and

2) deprotecting compound (8) with dilute aqueous acid at a temperature of about 50 to about 90°C to generate compound (4);

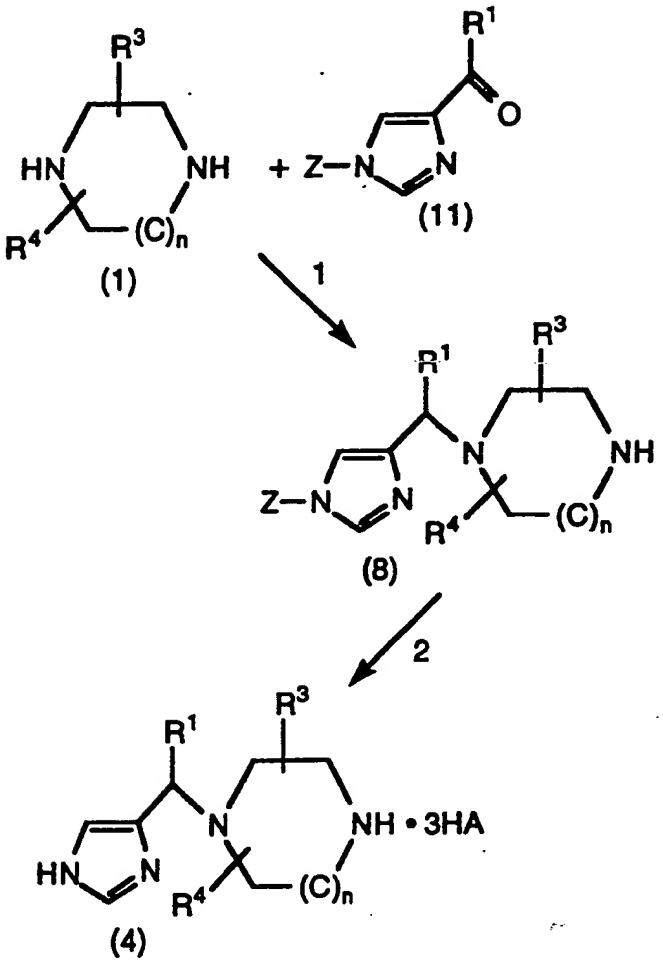
(C) Scheme 3



1) reacting compound (9), wherein Y is a protecting group, with compound (7) in an inert organic solvent at a temperature of about 20 to about 80°C to produce compound (10); and

2) deprotecting compound (10) with dilute aqueous acid at a temperature of about 50 to about 90°C to generate compound (4); or

(D) Scheme 4



1) reacting compound (11) with compound (1) in an inert organic solvent and in the presence of a reducing agent, at a temperature of about -20 to about 50°C, to produce compound (8); and

2) deprotecting compound (8) with dilute aqueous acid at a temperature of about 50 to about 90°C to produce compound (4).

INTERNATIONAL SEARCH REPORT

PCT/US 92/10697

International Application No

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 C07D233/54; A61K31/495; C07D403/06; A61K31/55

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl. 5	C07D ; A61K

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No.[13]
A	US,A,4 767 778 (J.M. ARRANG ET AL.) 30 August 1988 cited in the application see the whole document & EP,A,0 214 058 (INSERM) ---	1,15-19
A	WO,A,9 117 146 (INSERM) 14 November 1991 see the whole document ---	1,15-19
A	EP,A,0 338 939 (INSERM) 25 October 1989 cited in the application see the whole document ---	1,15-19
A	EP,A,0 197 840 (INSERM) 15 October 1986 cited in the application ---	1,15-19

-/--

° Special categories of cited documents :[10]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
05 MARCH 1993	17. 03. 93
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	DE JONG B.S.

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0 289 227 (SYNTEX PHARMACEUTICALS) 2 November 1988 see the whole document & US,A,4 935 417 cited in the application	1,15-19

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 92/ 10697

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claims 16 and 18 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO.

US 9210697
SA 68034

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information. 05/03/93

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		US-A- 5091428	25-02-92